Two Hurt More Than One: Severe Hyponatraemia and Rhabdomyolysis as Presenting Features of Addison's Disease

Luca Foppiani[1,*], Christian Cascio[1], Paola Pesce[2], Giancarlo Antonucci[1]

ABSTRACT

Addison's disease (AD) is characterized by non-specific symptoms and electrolyte disorders, namely hyponatraemia and hyperkalaemia; rhabdomyolysis is uncommon. AD may manifest at onset with a life-threatening adrenal crisis which is triggered by stressful events. We describe the case of a young man who was hospitalized for severe myalgia and fatigue. Severe hypotonic hyponatraemia, rhabdomyolysis and hypotension were found; hormonal assessment unexpectedly revealed primary adrenal insufficiency. Saline infusion and intravenous hydrocortisone significantly improved the patient's condition and normalized sodium and muscle enzyme levels; thereafter, he was switched to oral steroid therapy. The autoimmune origin of AD was ascertained by the positivity of adrenal cortex autoantibodies and 21b-hydroxylase autoantibodies. The association of hyponatraemia and rhabdomyolysis may be the initial finding of an as yet unknown AD, which requires proper investigation and treatment.

KEYWORDS

Addison's disease; rhabdomyolysis; hyponatraemia; myalgia; autoimmune adrenalitis

AUTHOR AFFILIATIONS

[1] Internal Medicine, Galliera Hospital, Genoa, Italy
[2] Autoimmunity Laboratory, San Martino Hospital, Genoa, Italy
* Corresponding author: Internal Medicine, Galliera Hospital, Mura delle Cappuccine 14, 16128 Genova, Italy; luca.foppiani@galliera.it

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INTRODUCTION

AD is an uncommon (incidence of 4–6 cases/million/year) and frequently overlooked disease (1–3); the autoimmune form is predominant. AD is manifested through the gradual onset of general symptoms present in many other conditions, so that its diagnosis is often delayed and formulated only in the presence of an adrenal crisis. Electrolyte disturbances such as hyponatraemia and hyperkalaemia (1–4) are characteristic of this disease. Rhabdomyolysis is an uncommon finding in AD (5–13), but is often overlooked, since muscle enzyme evaluation is not routinely performed.

We report the case of a young man suffering from worsening muscle aches and fatigue with biochemical findings of severe hyponatraemia and rhabdomyolysis, which led to an unexpected diagnosis of primary adrenal insufficiency of autoimmune etiology.

CASE REPORT

A 26-year-old man was taken to the Emergency Department (ED) of our hospital owing to worsening myalgia involving the lower limbs and fatigue over the previous three months. At that time, he had been evaluated in the ED of another region, owing to nausea and vomiting; severely reduced serum sodium levels (122 mEq/L), potassium levels in the upper normal range and hypotension (85/50 mm Hg) were found. On that occasion, the infusion of saline supplemented with sodium chloride raised sodium levels (129 mEq/L). The patient was discharged with the diagnosis of acute gastroenteritis.

On admission to our ED, the patient was alert, apyretic, and dehydrated. He reported that he was not taking any medication. Blood pressure (BP) was low (90/50 mm Hg), whereas oxygen saturation (98%), heart rate (60 bpm) and lung and abdominal examination were normal. Electrocardiogram and chest X-ray were unremarkable. Venous haemogas analysis showed partially compensated metabolic acidosis with normal anion gap: pH: 7.34, pCO_2: 33.4, HCO_3^-: 19, hyponatraemia: 113 (n. v. 135–145) and hypochloraemia: 83 (n. v. 98–106).

Blood chemistry confirmed the severe hyponatraemia (113 mmol/l) and revealed rhabdomyolysis characterized by increased serum creatine phosphokinase (CPK) and CPKMB levels (2% of total CPK) with normal troponin T levels, and lymphocytosis; creatinine was normal, and potassium was in the high-normal range (Table 1). Following the infusion of 500 ml of saline, the patient was transferred to our internal medicine ward in the late afternoon.

On physical examination, the patient was seen to be thin (BMI: 19 kg/m^2); hypotension was confirmed (90/60 mm Hg), with a further reduction (70/50 mm Hg) during orthostatism. He reported a weight loss of 5 kg during the last few months.

A diagnostic work-up for hyponatraemia was immediately carried out, including evaluation of adrenal gland and thyroid function, uric acid levels, spot urinary sodium levels and urine osmolarity. The urine data, ready available, were 34 mmol/l and 360 mOsm/kg, respectively.

In addition, blood sample was collected to uncover an autoimmune or infectious (cytomegalovirus, Epstein Barr virus, hepatitis B and hepatitis C, immunodeficiency virus) aetiology of rhabdomyolysis.

Afterwards, 500 ml of saline supplemented with 40 mEq of sodium chloride followed by 500 ml of normal saline were infused.

The morning after admission, a closer patient's assessment highlighted hyperpigmentation of both the outer border of the tongue, nail beds and elbow skin.

New blood chemistry confirmed profound hypotonic (serum osmolarity: 233 mOsm/kg) hyponatraemia (116 mmol/l); rhabdomyolysis had significantly worsened in comparison with the admission values, myoglobin levels were four times the upper normal value, uric acid level was in the low-normal range, and potassium levels were in the upper normal range (Table 1). Thyroid function showed a mild increase in TSH levels and normal FT4 levels (Table 1). Autoimmune and infectious tests for rhabdomyolysis were negative.

Remarkably, serum cortisol levels proved nearly undetectable (0.8 μg/dl) and were associated to hugely increased ACTH levels (1500 pg/ml); further rapid evaluation showed markedly increased supine renin levels, aldosterone levels in the low-normal range and severely decreased DHEAS levels (Table 1). The pituitary-gonadal axis was normal (Table 1), and thyroid autoantibodies were negative. Since hormonal results indicated primary adrenal insufficiency and the patient was hypotensive, he was immediately treated with 100 mg intravenous (i. v.) hydrocortisone, which was subsequently administered every 8 hours for two days and then progressively tapered to 50 mg two times a day, together with continuous normal saline infusion (1500 ml/day); accordingly the patient's condition and BP significantly improved.

Before starting hydrocortisone, blood sample was collected for evaluation of adrenal cortex autoantibodies (ACA) and 21b-hydroxylase autoantibodies (21-OH Ab). After a few days of i.v. hydrocortisone therapy, the patient was switched to oral therapy with cortisone acetate (25 mg at 8 a.m., 12.5 mg at 1.00 p.m. and 12.5 mg at 6 p.m.) and 0.05 mg fludrocortisone at 8 a.m. Five days after the beginning of i.v. steroid therapy, sodium, CPK, lymphocyte count and TSH levels normalized, and potassium levels settled in the middle of the normal range.

Both ACA: 1:20 by means of indirect immunofluorescence (Figure 1) and 21-OH Ab: 12 U/ml (n. v. < 0.4) proved positive; accordingly an autoimmune aetiology of the adrenal insufficiency was proved. Autoimmune polyendocrinopathies type 1 and type 2 were excluded by hormonal (Table 1) and physical evaluation. Anti-gastric parietal cell antibodies and anti-transglutaminase antibodies were absent. The patient was eventually discharged in good condition, and the dose of cortisone acetate was reduced to 43.5 mg per day; he was instructed on how to increase glucocorticoid therapy during stressful events, or to switch to parenteral hydrocortisone when required.

Hormonal and biochemical data of patient throughout hospitalization and follow-up are shown in Table 1.

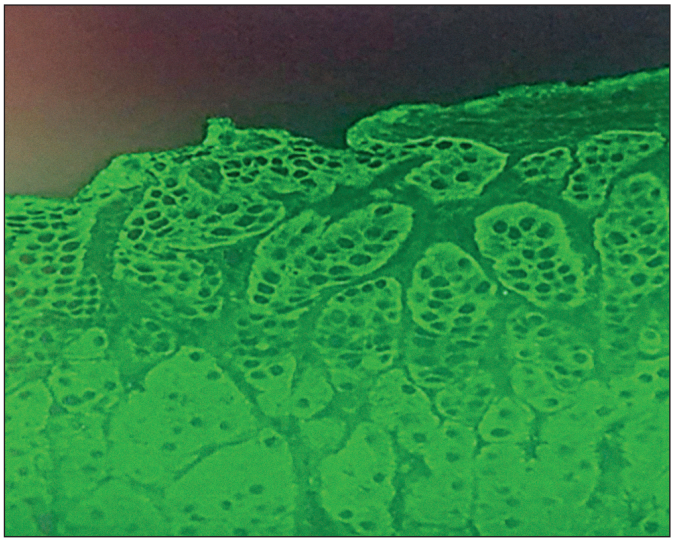

Fig. 1 Indirect immunofluorescence (1:20 dilution of patient's serum) on human unfixed adrenal tissue showing adrenal cortex autoantibodies (ACA) positivity in the adrenal glomerular zone.

APPENDIX

One month after discharge, the patient was hospitalized in another region owing to fever and diarrhoea. Blood chemistry showed neutrophilic leucocytosis (12400/mm^3 [n. v. 4000–9300]), increased C reactive protein and severe hypokalaemia (Table 1). Stool culture was positive for Salmonella, and a diagnosis of gastroenteritis was made. Saline, 100 mg i.v. hydrocortisone every 8 hours, i.v. potassium and 2 g ceftriaxone were started, eliciting rapid improvement of the patient's clinical condition and normalization of potassium levels. Hydrocortisone was tapered to 50 mg i.v. three times a day, and eventually oral steroid therapy was restarted. The patient was subsequently discharged and scheduled for follow-up where he is well and has normal BP and electrolyte levels (Table 1); the dose of cortisone acetate was reduced to 37.5 mg per day.

Tab. 1 Hormonal and biochemical evaluation of patient throughout hospitalization and follow-up.

	DAY 0 Our emergency department admission	DAY 1 start of steroid therapy	DAY 2	DAY 3	DAY 4	DAY 7 discharge	DAY 17 follow-up	DAY 37 Another hospital admission	DAY 57 Follow-up	DAY 112 Follow-up
glycemia (mg/dL)	122 (not fasting)	81	68	83		79	81	72	77	
Hb (14.2–17 gr/dL)	15.4	14.9	14.2	12.3		11.6	12.6	12.9	15.1	15.2
lymphocyte count (10^9/L) (1.13–3.37)	5010	4000	3170	2560		4240	3060		2400	2790
C-reactive protein (0–0.5 mg/dL)	0.1	0.3		0.1				11		
Na (135–145 mEq/L)	113	116	119	124	131	138	137	143	141	141
K (3.5–5 mEq/L)	4.6	4.9	4.9	3.8	3.7	3.8	3.9	2.7	4.1	3.9
creatinine (0.7–1.2)	0.9	0.7	0.7	0.7	0.6	0.8		0.8		
uric acid (3.5–7 mg/dL)	3.5									
calcium (8.2–10.2 mg/dL)	9.7	9.2	8.8			8.9				
CPK (39–308 UI/L)	1042	6652	3897		317	37	52			
myoglobin (28–72 ng/ml)	285									
ACTH (4.5–48 pg/mL)		1500					361.4		74.2	112
cortisol (6.2–19.4 µg/dL)		0.8								
DHEAS (160–449 µg/dL)		26.8								
supine renin (2.4–29 µU/mL)		500					68			75.7
supine aldosterone (3–15 ng/dL)		3.4								
FT4 (0.93–1.7 ng/dL)		1.68					1.56			
TSH (0.27–4.2 µU/mL)		6.77			1.7		3.1			3.0
PTH (15–50 pg/mL)			14.7		19.1				37.3	
calcium (8.5–10.5 mg/dL)	9.7	9.2	9.2		8.8	8.9			10	
25-OHD (> 30 ng/mL)			15.1							
LH (1.7–8.6 mUI/mL)			6.1				3.9			
FSH (1.5–12.4 mUI/mL)			0.7				2.8			
PRL (4–18.4 ng/mL)			32.7				12.5			
testosterone (3–8 ng/mL)			5.7				6.7			8.0
SHBG (10–80 nmol/L)							60.5			

DISCUSSION

The symptoms of AD arise slowly and insidiously; they include fatigue, anorexia, nausea, weight loss and, more rarely, muscle aches (1–4). Under stressful circumstances that require increased cortisol output (infections, surgery, trauma), an addisonian crisis may occur and be life-threatening if not promptly recognized and properly treated (1–4).

The most common electrolyte disorders found in AD are hyponatraemia and hyperkalaemia (1–4) (Table 2). By contrast, rhabdomyolysis is rarely observed and often overlooked (5–13) (Table 2). Our patient attended ED owing to worsening myalgia, which had started three months earlier. At that time, he had been examined at the ED of another region because of vomiting and malaise, and was found to have severe hyponatraemia, which was treated with sodium chloride-supplemented saline. A diagnosis of acute gastroenteritis was made and no further investigations were carried out.

Evaluation at the ED of our hospital confirmed severe hyponatraemia together with rhabdomyolysis; in addition, hypotension was found.

The work-up for hyponatraemia showed reduced serum osmolarity and spot urine sodium levels suggestive of renal loss. Combining anamnestic reports, and biochemical and clinical findings indicated that this was a case of chronic hypotonic hypovolemic hyponatraemia.

In addition, the presence of recent weight loss and hyperpigmentation in typical areas of the body was highlighted; accordingly, the suspicion of primary adrenal insufficiency was put forward, and was confirmed by means of hormonal evaluation. The autoimmune aetiology of AD was ascertained by the the positivity of ACA and 21-OH Ab.

Up to 85% of patients with AD have (hypovolemic) hyponatraemia (4), and sodium levels may be as low as 88 mmol/l (3).

Hyponatraemia is related to two pathophysiological mechanisms: i) the major cause is the reduced/absent action of aldosterone on distal tubules and collecting ducts which causes renal sodium wasting and hypovolaemia. In this regard, spot urine sodium levels in our patient were compatible with activated natriuresis; ii) the additional cause is the increased ADH release secondary to both cortisol deficiency and hypovolemic state (14).

It is well known that cortisol is an inhibitor of ADH secretion; accordingly, hyponatraemia in AD is enhanced by retention of free water related to the inappropriate secretion of ADH (15). The ADH release may also be stimulated by the reduction of blood pressure and cardiac output signalled to the central nervous system by baroceptors located in the carotid sinus and in the aortic arch. Finally, increased renal sensitivity to ADH might be involved, as suggested by aquaporin-2 water channel up-regulation in glucocorticoid-deficient rats (14). On the hand, the euvolemic hyponatremia often ascertained in secondary adrenal insufficiency is basically related to ADH release secondary to cortisol deficiency.

In our patient, sodium levels slightly increased the day after sodium chloride-supplemented saline infusion was started, and progressively normalized with i.v. hydrocortisone and normal saline and subsequent oral steroid therapy.

In the absence of traumatic events or the use of myotoxic drugs and despite the presence of hyponatremia, the cause of the rhabdomyolysis in our patient was initially not so clear. Autoimmune and infective aetiologies were excluded. The slight increase in TSH levels ascertained was not deemed a relevant cause; TSH levels normalized spontaneously a few days after starting steroid therapy.

Rhabdomyolysis is characterized by muscle weakness and/or myalgia, with release into the bloodstream of myofibril enzymes such as CPK and myoglobin (16). It may range from asymptomatic to severe, including compartment syndrome or renal failure due to myoglobin cast formation with subsequent intratubular obstruction. In our patient, the rhabdomyolysis manifested with myalgia and muscle weakness and did not cause renal failure.

The association between rhabdomyolysis and adrenal insufficiency (primary or secondary) is uncommon and overlooked (17–26) (Table 2).

To our knowledge, rhabdomyolysis with adrenal failure without hyponatraemia has been observed in only four cases: in three cases, adrenal insufficiency was of secondary origin, and due to long-term glucocorticoid therapy (one case) (18) and to panhypopituitarism (2 cases) (21, 24), respectively; in the remaining case, it was of primary origin due to an autoimmune process (8). In order to explain rhabdomyolysis in secondary adrenal insufficiency, in which aldosterone function is preserved and sodium levels are often normal, two pathogenetic mechanisms have been put forward: i) impaired muscle perfusion due to relative hypotension (24); ii) altered glycogenolysis and/or impaired mitochondrial oxidative metabolism of the muscle cells (24).

The hyponatraemia-associated rhabdomyolysis has been related to two mechanisms i) the reduced osmolality of the extracellular fluid causes cell swelling and intracellular potassium release into the extracellular space, with a decrease in myocyte transmembrane potential and subsequent muscle breakdown and the release of CPK and myoglobin into the bloodstream; ii) abnormalities in the Na^+/Ca^{++} exchange pump in the cell membrane; as the sodium level in the extracellular fluid decreases, the Ca^{++} output, which is related to the Na^+ input, also falls. Accordingly, intracellular calcium build-up activates proteases and phospholipases that cause myolysis. The rate of decline in serum sodium concentration and the severity of hyponatremia are significantly associated with the severity of muscle injury (16).

In our patient, rhabdomyolysis initially worsened despite the slight increase in sodium levels following the infusion of sodium chloride-supplemented saline. Thereafter, with the initiation of i.v. hydrocortisone for AD and the continuation of normal saline infusion, muscle enzyme levels normalized in a few days and myalgia improved. Rhabdomyolysis was therefore deemed to be caused by the combination of both severe hyponatraemia and hypocortisolism.

A final consideration emerges from the patient's previous medical reports. The diagnosis of AD was delayed by

Tab. 2 Literature summary of clinical and hormonal data and sodium levels in patients with rhabdomyolysis and adrenal insufficiency.

Authors	Age/gender	CPK peak (IU/L)	Sodium (mEq/L)	ACTH (pg/ml)	Cortisol (mg/dl)	Adrenal insufficiency	Comorbid endocrinopathies
Mor et al.	44/F	1670	103	129.4	0.7	primary	nil
Egan et al.	63/F	21490	97	405	18.1 → 6.1	primary	nil
Wiltshire et al.	8/F	14950	118	87.3	2.9	primary	nil
Elias	22/M	4000	135	1280	0.8–2	primary	nil
Solter et al.	33/M	12560	125	1891.4	1.2	primary	nil
Lau et al.	40/F	30779	106	832	5.8	primary	nil
Muir et al.	22/M	> 25000	110	4400	2.9	primary	severe hypothyroidism
Martin-Campagne et al.	9/M	1043	120	1250	1.4	primary	autoimmune polyglandular syndrome type 2
Tahir et al.	68/F	5000	120	NR	NR	primary	hypothyroidism
Foppiani et al. (current case)	26/M	6652	113	1500	0.8	primary	nil
Robillon et al.	31/F	21800	NR	22	8	secondary	panhypopituitarism
de Witte et al.	48/M	438	normal*	low*	low*	secondary	nil
Sayarlioglu et al.	58/F	> 40000	94	NR	2.1	secondary	panhypopituitarism
Oki et al.	52/M	11902	118	23	2.6	secondary	nil
Rezvanfar et al.	30/F	50000	137	NR	4	secondary	panhypopituitarism
Foppiani et al.	66/F	4250	123–127	low*	2.5	secondary	panhypopituitarism
Soresi et al.	64/F	1377	121	17	1.4	secondary	panhypopituitarism
Kennedy et al.	55/F	62270	137	< 10	0.6	secondary	nil
Komatsu et al.	67/F	6968	118	3.1	0.7	secondary	nil
Zhou et al.	22/M	5898	126	3.4	1.2	secondary	panhypopituitarism

NR, not reported.
* value not reported.

at least three months; indeed at that time the patient had been evaluated in another hospital and the association of severe hyponatremia, potassium levels in the upper normal range, vomiting and hypotension was found. The combination of these biochemical and clinical findings, although not diagnostic, were highly suggestive of adrenal failure. This emphasises that a high clinical suspicion is mandatory, in order to avoid misdiagnosing AD.

In summary, our case reveals that the association of hyponatraemia and rhabdomyolysis may be the initial finding of an unknown AD, which can be life-threatening and therefore requires prompt diagnosis and proper treatment.

CONFLICT OF INTEREST

Informed consent was obtained by the patient. "The authors declare that there is no conflict of interest regarding the publication of this paper." No grants or funds were received.

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